# PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

To:

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# PCT

## WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

(PCT Rule 43*bis*.1)

Date of mailing
*(day/month/year)* see form PCT/ISA/210 (second sheet)

Applicant's or agent's file reference
see form PCT/ISA/220

**FOR FURTHER ACTION**
See paragraph 2 below

| International application No. | International filing date *(day/month/year)* | Priority date *(day/month/year)* |
|---|---|---|
| PCT/EP2004/003984 | 15.04.2004 | 15.04.2003 |

International Patent Classification (IPC) or both national classification and IPC
C07K14/315, C07K16/12, C07K19/00, C07K16/46, C12N5/12, C12N15/02, A61K39/09, C12Q1/68, G01N33/569,

Applicant
INTERCELL AG

1. This opinion contains indications relating to the following items:

- ☒ Box No. I Basis of the opinion
- ☒ Box No. II Priority
- ☒ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☒ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- ☐ Box No. VI Certain documents cited
- ☐ Box No. VII Certain defects in the international application
- ☐ Box No. VIII Certain observations on the international application

2. **FURTHER ACTION**

If a demand for international preliminary examination is made, this opinion will usually be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA"). However, this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notifed the International Bureau under Rule 66.1*bis*(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of three months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

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**WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY**

International application No.
PCT/EP2004/003984

**Box No. I Basis of the opinion**

1. With regard to the **language**, this opinion has been established on the basis of the international application in the language in which it was field, unless otherwise indicated under this item.

   ☐ This opinion has been established on the basis of a translation from the original language into the following language , which is the language of a translation furnished for the purposes of international search (under Rules 12.3 and 23.1(b)).

2. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application and necessary to the claimed invention, this opinion has been established on the basis of:

   a. type of material:

   ☒ a sequence listing

   ☐ table(s) related to the sequence listing

   b. format of material:

   ☒ in written format

   ☒ in computer readable form

   c. time of filing/furnishing:

   ☒ contained in the international application as filed.

   ☒ filed together with the international application in computer readable form.

   ☐ furnished subsequently to this Authority for the purposes of search.

3. ☒ In addition, in the case that more than one version or copy of a sequence listing and/or table relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

4. Additional comments:

**Box No. II Priority**

1. ☒ The following document has not been furnished:

   ☒ copy of the earlier application whose priority has been claimed (Rule 43*bis*.1 and 66.7(a)).

   ☐ translation of the earlier application whose priority has been claimed (Rule 43*bis*.1 and 66.7(b)).

   Consequently it has not been possible to consider the validity of the priority claim. This opinion has nevertheless been established on the assumption that the relevant date is the claimed priority date.

2. ☐ This opinion has been established as if no priority had been claimed due to the fact that the priority claim has been found invalid (Rules 43*bis*.1 and 64.1). Thus for the purposes of this opinion, the international filing date indicated above is considered to be the relevant date.

3. Additional observations, if necessary:

**Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability**

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application,

☒ claims Nos. 1,2,5-11,14-37 (all partially), 3,4,12,13 (all completely)

because:

☐ the said international application, or the said claims Nos. relate to the following subject matter which does not require an international preliminary examination *(specify)*:

☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. are so unclear that no meaningful opinion could be formed *(specify)*:

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

☒ no international search report has been established for the whole application or for said claims Nos. 1,2,5-11,14-37 (all partially), 3,4,12,13 (all completely)

☐ the nucleotide and/or amino acid sequence listing does not comply with the standard provided for in Annex C of the Administrative Instructions in that:

| | | |
|---|---|---|
| the written form | ☐ | has not been furnished |
| | ☐ | does not comply with the standard |
| the computer readable form | ☐ | has not been furnished |
| | ☐ | does not comply with the standard |

☐ the tables related to the nucleotide and/or amino acid sequence listing, if in computer readable form only, do not comply with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions.

☐ See separate sheet for further details

**Box No. IV Lack of unity of invention**

1. ☒ In response to the invitation (Form PCT/ISA/206) to pay additional fees, the applicant has:

   ☐ paid additional fees.

   ☐ paid additional fees under protest.

   ☒ not paid additional fees.

2. ☐ This Authority found that the requirement of unity of invention is not complied with and chose not to invite the applicant to pay additional fees.

3. This Authority considers that the requirement of unity of invention in accordance with Rule 13.1, 13.2 and 13.3 is

   ☐ complied with

   ☒ not complied with for the following reasons:

   **see separate sheet**

4. Consequently, this report has been established in respect of the following parts of the international application:

   ☐ all parts.

   ☒ the parts relating to claims Nos. Invention 1: claims 1,2,5-11,14-37 (all partially)

**Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement**

1. Statement

| | | | |
|---|---|---|---|
| Novelty (N) | Yes: | Claims | 14, 22-24, 29-37 |
| | No: | Claims | 1,2,5-11, 15-21, 25-28 |
| Inventive step (IS) | Yes: | Claims | |
| | No: | Claims | 1,2,5-11,14-37 |
| Industrial applicability (IA) | Yes: | Claims | 1,2,5-11,14-37 |
| | No: | Claims | |

2. Citations and explanations

   **see separate sheet**

**Re Item III.**

The search report was established only for the first invention (claims 1, 2, 5-11 and 14-37) and pursuant R. 66.1(e) PCT the international preliminary examination will be limited to the said searched subject-matter.

**Re Item IV.**

The separate inventions/groups of inventions are:

Invention 1: claims 1,2,5-11,14-37 (all partially)

An isolated nucleic acid molecule encoding a hyperimmune serum-reactive antigen or fragment thereof as defined in claim 1, but referring only to SEQ ID No. 1; a vector comprising said nucleic acid molecule; a host cell comprising said vector; a hyperimmune serum-reactive antigen comprising the amino acid sequence of SEQ ID No. 145; a fragment of the said hyperimmune serum-reactive antigen as defined in claim 14; a method of producing the said S. pneumoniae hyperimmune serum-reactive antigen or fragment thereof; a process for producing a cell which expresses the said S. pneumoniae hyperimmune serum-reactive antigen or fragment thereof; the use of the said nucleic acid molecule or the said hyperimmune serum-reactive antigen or fragment thereof for the manufacture of a pharmaceutical preparation; an antibody, or at least an effective part thereof which binds at least to a selective part of the said hyperimmune serum-reactive antigen or fragment thereof; a hybridoma cell line which produces the said antibody; a method of producing the said antibody; the use of said antibody for the preparation of a medicament for treating or preventing S. pneumoniae infections; an antagonist which binds to the said hyperimmune serum-reactive antigen or fragment thereof; a method of identifying an antagonist capable of binding to the said hyperimmune serum-reactive antigen or of reducing or inhibiting the interaction activity of the said hyperimmune serum-reactive antigen or fragment thereof; the use of the said hyperimmune serum-reactive antigen or fragment thereof for the isolation and/or purification and/or identification of an interaction partner; a process for in vitro diagnosing a disease or a bacterial infection based on determining the presence of the said nucleic acid sequence or the presence of the said hyperimmune serum-reactive antigen or fragment thereof; the use of said hyperimmune serum-reactive antigen or fragment thereof for the generation of a

peptide binding thereto i.e. an anticaline, for the manufacture of a functional nucleic acid i.e. an aptamer or a spiegelmer, or of a functional ribonucleic acid i.e. a ribozyme, an antisense nucleic acid or a siRNA.

Inventions 2-45: claims 1,2,5-11,14-37 (all partially)

Idem as invention 1, but each of the inventions 2-45 referring to one of the further SEQ ID Nos. mentioned in claim 1 together with its respective corresponding SEQ ID No. according to claim 11.

Inventions 46-121: claims 3-10,12,14-37 (all partially)

Idem as invention 1, but each of the inventions 46-121 referring to one of the SEQ ID Nos. mentioned in claim 3 together with its respective corresponding SEQ ID No. according to claim 12.

Inventions 122-133: claims 4-10,13-37 (all partially)

Idem as invention 1, but each of the inventions 122-133 referring to one of the SEQ ID Nos. mentioned in claim 4 together with its respective corresponding SEQ ID No. according to claim 13.

They are not so linked as to form a single general inventive concept (R. 13.1 PCT) for the following reasons:

1. The only identifiable technical feature that all inventions have in common is that they relate to surface expressed or secreted S. pneumoniae hyperimmune serum-reactive antigens.

2. Hoskins J. et al. (D1) , Tettelin H. et al. (D2), WO 02/083855 (D3) and WO 02/077021 (D4) disclose surface expressed or secreted proteins (antigens) of S. pneumoniae as well as the nucleic acids encoding the said antigens. As any antigen, upon immunisation and depending on the immunisation protocol will result in a hyperimmune serum specific for the immunogen, the feature of being hyperimmune serum-reactive is considered to be a feature inherent to any antigen, thus also those disclosed in D1 and D2. Regardless of the foregoing considerations, Nabors, G.S. et al. (D5), Bethe, G. et al. (D6), Wizemann, T.M. et al (D7) and Overweg, K. et al. (D8) all disclose different S. pneumoniae hyperimmune serum-reactive antigens as well as the nucleic acids encoding them. The said antigens were isolated using hyperimmune sera of patients that

recovered from a pneumococcal infection or from individuals otherwise exposed to S. pneumoniae.

3. In view of the prior art represented by D1-D8, the problem of the underlying application can be defined as the provision of further secreted or surface expressed S. pneumoniae antigens, namely of such antigens that are hyperimmune serum-reactive, as well as of nucleic acids encoding the said antigens and of different uses of the said antigens and nucleic acids.

4. Each of the inventions listed above represents an independent solution concerning the problem underlying the present application. Solution 1 is the provision of secreted or surface expressed S. pneumoniae hyperimmune serum-reactive antigen according to SEQ ID No. 145 as well as of the nucleic acid according to SEQ ID No. 1 encoding the said antigen. Each of the solutions 2-133 refers to a different secreted or surface expressed hyperimmune serum-reactive antigen and the nucleic acid encoding it, as defined in the listing of the inventions wherein the correspondence of the SEQ ID Nos. for the nucleic acids and the antigens are to be found in Tab. 1.

5. In view of the fact that secreted and surface expressed S. pneumoniae antigens are already known from the prior art including the explicit disclosure of hyperimmune serum-reactive secreted or surface expressed S. pneumoniae antigens; due to the otherwise essential differences in the primary structure of the different antigens and the nucleic acids encoding them; and due to the fact that no other technical features can be distinguished which, in the light of the prior art could be regarded as special technical features common to the above solutions, the IPEA is of the opinion that there is no single inventive concept in the sense of R. 13.1 PCT underlying the 133 solutions contained in the present application. Consequently, there is a lack of unity, and different inventions have been formulated as different subjects.

**Re Item V.**

1 The following documents are referred to in this communication:
D1 : WO 02/083855 A (CHAKRAVARTI DEB NARAYAN ; RUSSELL DAVID PARRISH (US); WOOTERS JOSEPH L) 24 October 2002 (2002-10-24)
D2 : WO 02/077021 A (CHIRON SPA ; MASIGNANI VEGA (IT); FRASER

CLAIRE (US); TETTELIN HERVE () 3 October 2002 (2002-10-03)

D3 : HOSKINS J ET AL: "Genome of the Bacterium Streptococcus pneumoniae Strain R6" JOURNAL OF BACTERIOLOGY, WASHINGTON, DC, US, vol. 183, no. 19, October 2001 (2001-10), pages 5709-5717, -& EMBL accession no. AE008385 (7 September 2001)

D4 : TETTELIN H ET AL: "Complete genome sequence of a virulent isolate of Streptococcus pneumoniae" SCIENCE, AMERICAN ASSOCIATION FOR THE ADVANCEMENT OF SCIENCE,, US, vol. 293, no. 5529, 2001, pages 498-506, -& EMBL accession no. AE007318 (31 July 2001)

2.1 The present application does not meet the criteria of Art. 33(1) PCT, because the subject-matter of claim 1 is not new in the sense of Article 33(2) PCT.
D1-D4 disclose nucleic acids comprising SEQ ID No. 1 (**D1:** SEQ ID No. 209 and claim 1; **D2:** SEQ ID No. 4715 and claim 6; **D3:** EMBL accession no. AE008385; and **D4:** EMBL accession no. AE007318).

2.2 Furthermore, the following claims lack novelty over the following documents:

- claims 2, 5-11, 15, 16, 20, 21 and 25-27 over **D1** (supra and SEQ No. 424; p. 85, l. 15 - p. 108, l. 4; claims 2-11, 25-28, 59-71);
- claims 2, 5-11, 15-21 and 25-28 over **D2** (supra and SEQ ID no. 4716; p. 8, l. 30 - p. 34, l. 40; claims 1-16);
- claims 2, 5, 7 and 11 over **D3** (supra);
- claims 2, 5, 7 and 11 over **D4** (supra)

2.3 The subject-matter of claims 14, 22-24 and 29-37 is novel over the prior art as there is no document available that discloses the combination of features suggested by the said claims (Art. 33(2) PCT).

3.1 The fragments suggest by claim 14 appear to be arbitrary fragments of the antigen according to SEQ ID No. 145 which are not associated with any surprising technical effect. As the said antigen is already known from the prior art (cf. 2.2 herein above) the said fragments are not considered to be based on an inventive step (Art. 33(3) PCT).

3.2 The subject-matter of claims 22-24 and 29-37 refer to routine applications once the gene or antigen is known as in the present case (cf. 2. herein above) which thus do not establish an inventive step (Art. 33(3) PCT).

4. The subject-matter of claims 1, 2, 5-11 and 14-37 appears to be industrially applicable (Art. 33(4) PCT).

5.1 The wording of the restriction of claim 1(e) ("but for the degeneracy of the genetic code") lacks clarity and therefore causes problems in construing the scope of claim 1 (Art. 6 PCT). For the purpose of examination it was disregarded.

5.2 In claim 14 the reference to "predicted immunogenic aa" and "location of identified immunogenic region" in Tab. 2 is not clear as these expressions are present neither in said Table nor in the legend thereto (Art. 6 PCT). The passage of said claim using these expressions was therefore considered to refer to fragments as defined by the last three columns of Tab. 2.